“Studies on Synthesis and Characterization of Quinoline Derivatives as Metal Chelates and Their Applications”

A Synopsis Submitted to

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CHEMISTRY
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Submitted by

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Title of the Proposed Research Work:

"Studies on Synthesis and Characterization of Quinoline Derivatives as Metal Chelates and Their Applications"

Introduction:

Quinolines were first discovered from coal tar by Friedlieb Ferdinand Runge in 1834 [1].After half century Skraup- Doebner–Miller successfully synthesized the quinolines in laboratory [2]. For 180 years many synthetic protocols and applications have been developed based on the Skraup transformation because of its simplicity and the importance of the quinoline itself [3].

Quinoline derivatives are used as drugs for different diseases such as tuberculosis, schizophrenia and malaria [4-5]. Apart from its medicinal value quinoline derivatives are also studied as a supramolecular host [6].

The chemistry of quinoline and its derivatives has attracted special interest due to their therapeutic properties. Quinoline sulphonamides have been used in the treatment of cancer, tuberculosis, diabetes, malaria, and convulsion. Apart from the magnetic and photophysical properties of Quinoline derivatives also exhibits the bioactivities of lanthanides such as antimicrobial [7], antitumor, antivirus, anticoagulant action.

In the recent time, quinoline nucleus has gathered an immense attention among chemists as well as biologists as it is one of the key building elements for many naturally occurring compounds [8]. Among the class of Quinoline derivatives 8-hydroxyquinolines have been explored as a viable drug discovery platform in many instances. Metal complexes of 8-hydroxyquinoline as a primary ligand can exhibit biological activity because many more transition metal complexes and in particular those with N-and O-donor atoms have been known to have antimicrobial properties [9].

It can exert their physiological properties through bidentate chelation of metal ions [10]. It is evident that formation of chelates metal ions increases the lipophilicity of the bioactive compounds through diverse array of biological redox mechanism for the effective permeability of the compounds into the site of action.

Tremendous work based on the synthesis and development of metal complexes of 8-hydroxyquinolines [11-13]. Various strategies can be envisaged to synthesize or modify metal complex structures by exploiting the reactivity of this heterocycle with their derivatives by various researchers [14]. 8-hydroxyquinoline and its derivatives were also reported to have promising bioactivities, including anticancer [15], antibacterial [16],antidyslipidemic andantioxidative properties [17], vascorelaxing properties [18], antivirus and antiplateletactivities [19].

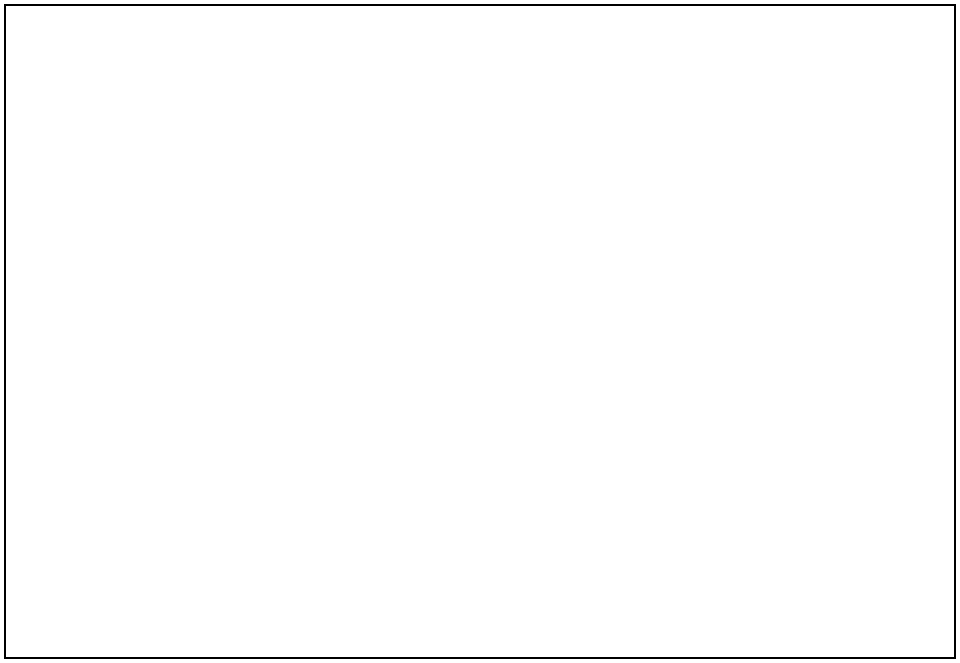

Figure1: Various Biological Properties of Substituted Quinoline Derivatives

Research Problem:

The theme of the proposed research workis synthesis of quinoline derivatives as metal chelatesbecause; it has fundamental importance in various fields such asmedical, agriculture, analytical, biological and industrial field. Its application has found in biochemistry, material science and natural product synthesis.

Recently, in day to day life the scientist communities are trying to synthesize novel bioactive compounds which are beneficial to society. In the recent time, quinoline nucleus has gathered an immense attention among chemists as well as biologists because building elements for many naturally occurring bioactive compounds [20][21].

Significance of Research Work:

The increased life expectation in various countries, represent a major burden onhealthcare systems around the world. There are over 35 million people worldwide displaying dementia symptoms and this number is expected to double by 2030 (65.7 million) and more than triple by 2050 (115.4 million) [22]. Dementias are progressive pathophysiological disorders characterized by neuronal cell loss and severe cognitive impairment [23].

Alzheimer's disease (AD) is the most common type of dementia. Alzheimer's disease (AD) is characterized by oxidative stress, misfolded proteins, neuronal cell loss, and eventually death [24-25].

The ligands 8-hydroxyquinoline and their derivatives formcomplexes with Cu (II) which inhibit peptide aggregation.Cu (II), Zn (II) and Fe (III) exhibit a relatively high binding affinity with α β-peptide [26], and induce the formation of toxic oligomers and reactive oxygen species (ROS) leading to oxidative stress [27].

TB remains one of the world's deadliest communicable diseases. *Mycobacterium tuberculosis*, the pathogen responsible for tuberculosis (TB). In 2014, an estimated 9.0 million people developed TB and 1.9 million died from the disease, 360,000 of whom were HIV-positive. Multidrug-resistant TB strains (MDR-TB) are a great worldwide problem. Drug resistance surveillance data indicate that in 2014approximately 480,000 people developed MDR-TB worldwide. Among TB patients reported by national TB programme in 2014, there were an estimated480,000 cases of MDR-TB. Extensively drug-resistant TB (XDR-TB, defined as MDR-

TB plus resistance to any fluoroquinolone and any second-line injectable drugs) has been identified in 105 countries globally in 2014 [28], and the average proportion of MDR-TB cases with XDR-TB was 9.7%.

The best known quinoline anti-TB derivativebedaquiline (Sirturo™)is a new class of antitubercular drugs belonging to diarylquinolines, was approved by FDA for treatment of MDR-TB. Structural modifications of quinolines by various groups have led to the identification of potent anti-TB compounds exhibiting significant activity especially against strains of M. tuberculosis [29-30].It was found that these anti-TB quinolines exhibit various mechanisms of action; for example, they inhibit mycobacterial ATP synthase [31],mycobacterial FtsZ protein [32], glutathione S-transferase [33], enoyl-ACP reductase or decaprenylphosphoryl-b-D-ribose-20-epimerase; also other sites of actions of 8-hydroxyquinolines can be found due to the bidentate metal-chelating property.

Potential significance of quinoline derivativesgrowing interest in scientific community and motivated to opportunity for my research work.

Given the background and motivation, I would like to focus on quinoline derivatives and their metal complexes has potential applications in various fields.

Brief Review of Literature:

After literature survey to the best of our knowledge showed that **t**remendous work based on the synthesis and development of metal complexes of 8-hydroxyquinolines yet to explore. 8-hydroxyquinoline and its derivatives were also reported to have promising bioactivities, including anticancer, antibacterial, and antivirus activities.

In the synthesis of Schiff bases from 8-hydroxyquinoline derivatives as potential antidyslipidemic agents. Towards an ongoing drug discovery research for developing novel antidyslipidemic drugs, several drugs are being used in the treatment of dyslipidemia. The drugs can intervene by lowering cholesterol (LDL and total cholesterol) or by lowering triglyceride levels in plasma.

In addition, 8-hydroxyquinoline and its Schiff bases are able to inhibit the growth of several animal tumors, and some metal chelates have shown good antitumor activities against animal tumors.

DNA is an important cellular receptor, many chemicals exert their antitumor effects by binding to DNA thereby changing the replication of DNA and inhibiting the growth of the tumor cells [34], which is the basis of designing new and more efficient antitumor drugs and their effectiveness depends on the mode and affinity of the binding.

Some of the quinoline derivatives and their analogues/isosteres such as 8-hydroxyquinoline also showed significant herbicidal activities. 8-hydroxyquinoline- 2-carboxanilides and therederivatives were tested for their activity related to inhibition of photosynthetic electron transport (PET) in spinach (*Spinaciaoleracea*L.) chloroplasts.

After review of various methods for the synthesis of Quinoline Derivatives as Metal Chelates and Their Applications, it was found that they have very much attention of international and national researchers.

OBJECTIVES OF RESEARCH STUDY:-

The objective of research is an increasing interest in designing and synthesis of substituted Quinolinederivatives as chelate and their metal complexes. Thus, substituted Quinoline metal complexes compounds having wide applications in pharmaceuticals and

material industries. Keeping this in mind, the objectives of research work will be synthesis of various substituted Quinoline compounds and investigate their applications in various fields.

Outline of the Proposed Research Work

The proposed work will be completed in four parts

Phase-I

In first phase, the extensive collection of references, along with literature survey, synthesis of starting material, intermediate compound and purification of solvent will be done.

Phase-II

In the second phase the maximum attention will be paid on the synthesis of and characterization of substituted quinoline derivatives which acts as metal chelates.

Phase-III

The third phase covers the synthesis and characterization metal complexes. The Synthesized compounds will be characterized on the basis of techniques like IR, ^{1}H NMR, ^{13}C NMR, XRD, UV spectral study, Mass Spectroscopy, etc.

Phase-IV

In fourth phase, the suitable application of the synthesized compounds will be investigated.

The work carried out under these schemes will be submitted in the form of thesis for the award of Ph.D. degree in chemistry.

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